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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/027,654	02/23/1998	JEFFREY KENNETH HORTON	28911/34561	3465

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/027,654	HORTON, JEFFREY KENNETH	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003 and 31 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-14, and 16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/31/03 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 3/17/03 in Paper No. 24 is acknowledged and have been entered. Claims 1, 14, 18, and 20 have been amended. Accordingly, claims 1-2, 4-14, and 16-21 are pending and are under examination.

Claim Objections

3. Claims 17 and 19 are objected to for being substantial duplicates of each other. Appropriate correction is required.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

4. In light of Applicant's amendment, the rejection of claims 1-2, 4-14, and 16-21 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

5. In light of Applicant's amendment, the rejection of claims 1-2, 4-5, 8, 10, 14, 16-18, and 20 under 35 U.S.C. 102(b) as being anticipated by Khanna (US 5,032,503), is hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2, 4-5, 8, 10, 14, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lundin (US Patent 5,558,986) in view of Khanna (US Patent 5,032,503).

Lundin discloses a method and kit for ATP assays using cyclodextrin. Lundin teaches mixing the sample of cells with a lysis reagent (extractant) to generate a lysed cellular sample in order to extract intracellular analyte from the cells in the sample. Lundin teaches simultaneously contacting the lysed cellular sample with a sequestrant such as cyclodextrin, i.e. α, β, or γ cyclodextrin, to neutralize the effect of the lysis reagent (see Abstract and column 6, lines 38-49). The cell lysis reagent is a detergent or surfactant such as dodecyl trimethyl ammonium bromide (see column 2, lines 43-45 and Example 1). Cyclodextrin sequesters or neutralizes the lysis reagent by forming a

complex with it so that it is possible but not necessary or desirable to remove the complex from the solution (see column 5, lines 33-52 and column 6, lines 55-67). Cyclodextrin is preferably used in excess of the surfactant on a molar basis considering the stoichiometry of inclusion complex that is formed (see column 7, lines 13-37). The cyclodextrin can be added at any step in the assay method after completion of lysis but always before or simultaneously with the addition of components (enzymes) involved in the assay (column 7, lines 28-38). Analytes extracted from cells include intracellular metabolites such as ATP and nucleic acids. Lundin further discloses a kit for lysis and assay of analytes, i.e. ATP comprising a lysis reagent, a cyclodextrin, reagent i.e. firefly luciferase reagent, and an assay buffer (see column 7, lines 3-13).

Lundin differs from the instant invention in failing to disclose mixing the lysed and neutralized cellular sample with specific binding assay reagent, i.e. specific binding partner for the intracellular analyte and tracer, to perform a specific binding assay.

Khanna et al. disclose a specific binding assay for determining the presence of analyte in a cell sample (see column 3, lines 11-20 and column 2, lines 50-54). Khanna et al. disclose mixing the cell sample with a detergent (surfactant), i.e. dodecyltrimethylammonium bromide, specific binding partners for the analyte (anti-analyte antibody, enzyme-analyte conjugate), and cyclodextrin to initiate complex formation, whereby the presence of analyte and specific binding partner reaction is indicative of the presence of the analyte in the sample. Khanna et al. teach labeling the specific binding partners with a tracer, i.e. fluorescer, enzyme (see column 3, line 21 to column 4, line 4). Khanna et al. disclose that cyclodextrin is not added to the detergent

and specific binding partners for the analyte, prior to the addition of the sample; thus, cyclodextrin is added to a reaction mixture initially formed by the combination of the cell sample, the detergent, and the specific binding partners for the analyte (see column 5, lines 12-32). Cyclodextrin is added in a sufficient amount to neutralize the detergent and allow complex formation between the specific binding partners. Cyclodextrin concentrations including an amount of 1-5% of the reaction mixture is set forth in column 4, lines 37-58. Khanna et al. also disclose a kit suitable for diagnostic immunoassay of the analytes comprising a detergent, cyclodextrin, specific binding partners, assay buffers, drying agents, and excepients, i.e. to remove materials as in unbound tracers (see column 7, lines 37-60).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform a specific binding assay as taught by Khanna on the intracellular analyte extracted from the lysed sample of Lundin because both of Lundin and Khanna use cyclodextrin to neutralize the effect of a detergent, and Lundin specifically taught using detergent at concentrations that lyse cells so as to extract intracellular analyte for use in an assay, and further taught that cyclodextrin has the ability to reduce, obviate, or overcome interference caused by the detergent at such concentrations, to subsequent assays such as enzyme assay, or specific binding assay as taught by Khanna, of the extracted intracellular analyte.

7. Claims 7 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lundin (US Patent 5,558,986) in view of Khanna (US Patent 5,032,503) as applied

to claims 1-2, 4-5, 8, 10, 14, and 16-20 above, and in further view of Brown et al. (US 5,739,001).

Lundin and Khanna et al. have been discussed supra. Lundin and Khanna et al. differ from the instant invention in failing to disclose that the cells are cultured, lysed, and assayed in a single vessel and in the presence of the culture medium. Lundin and Khanna et al. further differ in failing to disclose assaying for cyclic AMP.

Brown et al. disclose a specific binding assay (cell-based assay) for determining the presence of cell-related analyte in a cell sample. Specifically, Brown et al. disclose mixing the cell sample (whole blood) with a lysis reagent to lyse red blood cells in the sample. Brown et al. also disclose mixing the lysed cellular sample with a specific binding partner for the analyte, i.e. anti-LTC_4 antibody for Leukotriene C_4, in order to form analyte-specific binding partner complexes whereby the presence of analyte and specific binding partner complexes is indicative of the presence of the analyte in the sample. See Example 2 and column 3, lines 18-42. Other analytes that can be detected using this method include adenosine-3', 5'- cyclic monophosphate (cyclic AMP) and cytokines, i.e. interleukin-6 (see column 4, lines 59-64). Brown et al. disclose that the assay is a homogeneous assay that is performed in a single reaction vessel (cells are not attached to solid phase for assay) (see column 4, lines 5-12 and lines 38-56). The cells are cultured, lysed, and assayed in the same vessel; thus, eliminating the need for a separate culturing step (see column 3, line 66 to column 4, line 1). The specific binding partners can be immune type, i.e. antibody or non-immune type, i.e.

biotin/avidin (see column 5, lines 12-38). Brown et al. also disclose labeling the specific binding partner with a tracer or label, i.e. ^{3}H and ^{125}I (see column 6, lines 5-16).

One of ordinary skill in the art at the time of the instant invention would have been motivated to culture and lyse cells to extract intracellular analyte in a single reaction vessel as taught by Brown for specific binding assay such as taught by Lundin and modified by Khanna, because both of Lundin and Khanna specifically taught that cyclodextrin for use with lysis detergent in an assay mixture within a reaction vessel, has the advantage of neutralizing the effect of the lytic detergent such as in the method of Brown; thus, providing a capability to detect both intracellular and cell-surface analytes, from samples grown in a cell culture medium in a single reaction vessel and eliminating the need for a separate "culturing step" and "separation step", that would have been otherwise required.

8. Claims 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lundin (US Patent 5,558,986) in view of Khanna (US Patent 5,032,503) as applied to claims 1-2, 4-5, 8, 10, 14, and 16-20 above, and in further view of Cook (2) (WO 94/26413).

Lundin and Khanna et al. have been discussed supra. Lundin and Khanna et al. differ from the instant invention in failing to teach a multiwell plate. Lundin and Khanna et al. further differ in failing to teach scintillation proximity assay.

Cook (2) discloses an apparatus and method for studying cellular processes using scintillation proximity assay. The apparatus comprises a vessel having a base

with a scintillant substance and which is adapted for attachment and growth of cells (see Abstract). Cook (2) further discloses a multiwell plate comprising an array of wells held in fixed relationship to one another wherein each well is a vessel (see page 10, first full paragraph). The multiwell plate can take various formats for the purpose of culturing cells using standard cell culture media and growing cells in a sterile environment at 37 C in a 95 % humidified air and 5% CO2 incubator as well as studying cellular biochemical processes in living cells (page 14, second and third full paragraphs and page 15, second full paragraph). Cook (2) disclose that a considerable advantage of the scintillation proximity assay is that it does not require separation of bound and molecular species from free, thereby minimizing handling of potentially hazardous substances (see page 7, second full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the scintillation proximity multiwell assay system having an array of reaction vessels as taught by Cook (2) into the specific binding assay as taught by Lundin and modified by Khanna because Lundin and Khanna specifically taught that cyclodextrin for use with lysis detergent in an assay mixture, has the advantage of neutralizing the effect of the lytic detergent within a single reaction vessel; thus, eliminating the need for a separate "culturing step" and "separation step", in high-throughput assays requiring minimal handling of materials as in the method of Cook (2).

9. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lundin (US Patent 5,558,986) in view of Khanna (US Patent 5,032,503) as applied to claims 1-2, 4-5, 8, 10, 14, and 16-20 above, and further in view of Edmonds (US 6,159,750).

Lundin and Khanna et al. has been discussed supra. Lundin and Khanna et al. differ from the instant invention in failing to teach that the specific binding assay is fluorescence polarization assay.

Edmonds discloses a specific binding assay for the detection of analytes, i.e. T4 hormone and Free Estriol, wherein reagents, i.e. antibodies or specific binding partners and labels, are mixed with the sample containing the analyte and are caused to react. Edmonds discloses using fluorescence polarization assay to detect and measure the concentration of the analyte in the sample. See Abstract, Example 2, and Example 4.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to detect the polarization characteristics of the specific binding assay taught by Lundin and modified by Khanna using fluorescence polarization assay as taught by Edmonds because Lundin and Khanna are generic with respect to the type of detection used in detecting the presence and amount of the analyte and Edmonds specifically taught that fluorescence polarization immunoassay is a common and conventional method of analyzing samples for the presence of analyte of interest.

Response to Arguments

10. Applicant's arguments with respect to claims 1, 2, 4-14, and 16-21 have been considered but are moot in view of the new grounds of rejection.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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